PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 95.80591/002	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001654	International filing date *(day/month/year)* 15.04.2004	Priority date *(day/month/year)* 15.04.2003
International Patent Classification (IPC) or national classification and IPC A61K51/04, A61P35/00		
Applicant ALGETA AS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.11.2004	17.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Skjöldebrand, C Telephone No. +49 89 2399-8467

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-39	as originally filed
Claims, Numbers	
1-20	received on 16.11.2004 with letter of 15.11.2004
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-13 (I.A. only)

   because:

   ☒ the said international application, or the said claims Nos. 1-13 (I.A. only) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14, 18-20
	No:	Claims	15-17
Industrial applicability (IA)	Yes:	Claims	14-20
	No:	Claims	1-13

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 2004/043487 A (BRACCO IMAGING SPA ; DE HAEEN CHRISTOPH (IT)) 27 May 2004 (2004-05-27)

D2: US 2001/008625 A1 (LARSEN ROY H ET AL) 19 July 2001 (2001-07-19)

D3: WO 01/60417 A (LARSEN ROY H ; ANTICANCER THERAPEUTIC INV S A (NO); HENRIKSEN GJERMUND) 23 August 2001 (2001-08-23)

D1: cf. Item VI below.

D2 discloses receptor conjugates with an antibody, a folate, and a radionuclide such as ^{227}Th (cf. claims 1-4) to be used in the treatment of different soft-tissue cancer forms (cf. claim 20). Kits where the radioligand and the antibody are separate are also described (cf. claims 22, 23).

D3 discloses conjugate systems comprising a liposome with a chelator, such as DOTA (cf. claim 3) and a heavy alpha-emitter such as ^{227}Th (cf. claim 12). The liposomes may be conjugated to antibodies and are useful in the treatment of various non-skeletal cancer forms (cf. claim 30). Kits where the liposomes, the radionuclide and the targeting molecule are in separate vials are disclosed (cf. claims 31, 32).

Novelty - Article 33(2) PCT

By the exclusion of liposomes, folate, antibodies etc. as recognition units in, novelty is

established over D2 and D3 for all the independent claims.

Inventive Step - Article 33(3) PCT

D2 and D3 are silent about the dosage of ^{227}Th. The high dosages as in the examples couldn't be derived from the prior art. Claims 1-14 and 18-20 appear to relate to inventive subject-matter.

An inventive step cannot be recognised for independent claims 15 and 17, as no dosage is referred to therein. The mere novelty-establishing exclusions of liposomes etc. are not sufficient to establish an inventive step over D2 and D3.

Industrial Applicability - Article 33(4) PCT

For the assessment of the present claims 1-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/043487	2004-05-27	2003-11-13	2002-11-14

D1 (WO 2004/043487) is an earlier filing (E-document) with a possible relevance for novelty in the European phase.

D1 discloses conjugates comprising ^{227}Th (claim 14) for the treatment of e.g. gastric tumours. The complexes have recognition units that appear to not belong to the excluded groups (bone-seekers, liposomes etc.). There is no disclosure on the dosage of the ^{227}Th.

D1 appears to interfere with novelty of independent claim 15.

80591002cls.doc

Claims

1. A method for the treatment of soft tissue disease in a mammalian subject, said method comprising administering to said subject a therapeutically effective quantity of a soft tissue targeting complex of thorium-227 and a complexing agent, wherein said quantity is such that an acceptably non-myelotoxic quantity of radium-223 is generated *in vivo* by nuclear decay of the administered thorium-227 wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments and wherein the therapeutically effective quantity of thorium-227 is at least 25 kBq/kg.

2. A method as claimed in claim 1 wherein said subject is human or canine.

3. A method as claimed in any one of claims 1 to 3 wherein said therapeutically effective quantity is at least 75 kBq of thorium-227 per kilogram bodyweight.

4. A method as claimed in any of claims 1 to 3 wherein said acceptably non-myelotoxic quantity is less than 300 kBq radium-223 per kilogram bodyweight.

5. A method as claimed in claim 4 wherein said acceptably non-myelotoxic is less than 150 kBq of radium-223 per kilogram bodyweight.

6. A method as claimed in any of claims 1 to 5 wherein said complex comprises chelated thorium-227 linked to a ligand selected from the group of antibodies, antibody constructs, antibody fragments, constructs of antibody fragments and mixtures thereof.

7. A method as claimed in any of claims 1 to 6 wherein said soft tissue disease is a malignant disease.

8. A method as claimed in claim 7 wherein the malignant disease is a disease selected from the group of carcinomas, sarcomas, myelomas, lukemias, lymphomas and mixed type cancers.

9. A method as claimed in any of claims 1 to 8 wherein said subject is also treated to combat the myelotoxicity of the radium-223 generated therein.

10. A method as claimed in claim 9 wherein said subject is provided with stem cell treatment.

11 A method for the treatment of soft tissue disease in a mammalian subject, said method comprising administering to said subject a therapeutically effective quantity of a soft tissue targeting complex of thorium-227 and a complexing agent, wherein said quantity is D_{add} as calculated from formula I below, such that an acceptably non-myelotoxic quantity D_{Ra} of radium-223 is generated *in vivo* by nuclear decay of the administered thorium-227;

$$D_{add} = \frac{D_{Ra} \times T_{Th}\left((T_{Bio})^{-1} + (T_{Th})^{-1}\right)}{1.65} \qquad (I)$$

wherein:

T_{Bio} is the biological half-life of said soft tissue targeting complex of thorium-227 and a complexing agent;

T_{Th} is the physical half-life of ^{227}Th (18.7 days);

D_{add} is the activity of the administered ^{227}Th complex (kBq/kg) and is is at least 25 kBq/kg; and

D_{Ra} is the acceptably non-myelotoxic amount of ^{223}Ra;

and further, wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

12. A method as claimed in claim 11 wherein D_{Ra} is 200 kBq/kg

13. A method as claimed in any of claims 1 to 12 in combination with at least one further treatment modality selected from surgery, external beam radiation therapy, chemotherapy, endoradionuclide therapy with radionuclides other than ^{227}Th, and/or tissue temperature adjustment.

14. A pharmaceutical composition comprising a soft tissue targeting complex of thorium-227 and a complexing agent, together with at least one pharmaceutical carrier or excipient wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments and wherein the thorium-227 is present at a therapeutically effective quantity of at least 25 kBq/kg.

15. A soft tissue targeting complex of thorium-227 and a complexing agent wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

16. A complex as claimed in claim 15 wherein thorium-227 is chelated by a derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid.

17. A method for forming a complex as claimed in claim 16 comprising heating said thorium-227 with said derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to form a chelated thorium-227 and subsequently attaching said chelated thorium-227 to a targeting moiety.

18. A kit for use in a method as claimed in any of claims 1 to 13, said kit comprising a solution of a soft tissue targeting complex of thorium-227 and a complexing agent together with instructions for the use of said solution in said method wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

20. A kit for use in a method as claimed in any of claims 1 to 13, said kit comprising a complexing agent capable of complexing thorium ions; where said complexing agent is not a soft tissue targeting complexing agent, a soft tissue targeting compound, optionally together with a linker compound, conjugatable to said complexing agent to yield a soft tissue targeting complexing agent; and instructions for the preparation therefrom of a soft tissue targeting complex of thorium-227 and a complexing agent, and optionally also for the use of said complex in said method wherein the soft tissue targeting complex is a moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

INTERNATIONAL SEARCH REPORT

International Application No
GB2004/001654

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/04 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/043487 A (BRACCO IMAGING SPA ; DE HAEEN CHRISTOPH (IT)) 27 May 2004 (2004-05-27) abstract claim 14	1-20
X	US 2001/008625 A1 (LARSEN ROY H ET AL) 19 July 2001 (2001-07-19) abstract claims	1-20
X	WO 01/60417 A (LARSEN ROY H ; ANTICANCER THERAPEUTIC INV S A (NO); HENRIKSEN GJERMUND) 23 August 2001 (2001-08-23) abstract claims	1-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2004	04/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/GB2004/001654

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MILENIC D E ET AL: "In vivo comparison of macrocyclic and acyclic ligands for radiolabeling of monoclonal antibodies with <177>Lu for radioimmunotherapeutic applications" NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 29, no. 4, May 2002 (2002-05), pages 431-442, XP004357346 ISSN: 0969-8051 the whole document	1-20
A	WO 01/66155 A (FRANK R KEITH ; SIMON JAIME (US); GULYAS GYONGYI (US); KIEFER GARRY E) 13 September 2001 (2001-09-13) the whole document	1-20
A	WO 02/05859 A (COCKBAIN JULIAN ; LARSEN ROY H (NO); ANTICANCER THERAPEUTIC INV S A (N) 24 January 2002 (2002-01-24) the whole document	1-20

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB2004/001654

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Ional Application No
.C., GB2004/001654

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004043487 A	27-05-2004	WO 2004043487 A1	27-05-2004
US 2001008625 A1	19-07-2001	NO 995978 A	07-06-2001
		AU 1743201 A	12-06-2001
		EP 1237584 A1	11-09-2002
		JP 2003515570 T	07-05-2003
		WO 0139806 A1	07-06-2001
WO 0160417 A	23-08-2001	NO 20000855 A	22-08-2001
		AU 3782701 A	27-08-2001
		BR 0108572 A	19-11-2002
		CA 2400994 A1	23-08-2001
		CN 1404402 T	19-03-2003
		CZ 20023164 A3	16-04-2003
		EP 1257299 A2	20-11-2002
		JP 2003522808 T	29-07-2003
		WO 0160417 A2	23-08-2001
		US 2001048914 A1	06-12-2001
		ZA 200206500 A	14-08-2003
WO 0166155 A	13-09-2001	AU 4906901 A	17-09-2001
		CA 2381123 A1	13-09-2001
		EP 1227849 A2	07-08-2002
		HU 0203743 A2	28-02-2003
		WO 0166155 A2	13-09-2001
		ZA 200200659 A	23-01-2003
WO 0205859 A	24-01-2002	NO 20003457 A	07-01-2002
		AU 6773401 A	30-01-2002
		CA 2413736 A1	24-01-2002
		EP 1296722 A2	02-04-2003
		WO 0205859 A2	24-01-2002
		JP 2004503331 T	05-02-2004
		US 2003166989 A1	04-09-2003